

PATHOPHYSIOLOGY AND ETIOLOGY OF CHRONIC RENAL DISEASE

The spectrum of kidney disease in American Indians

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The spectrum of kidney disease in American Indians. American Indians and Alaska Natives (AI/AN) experience high rates of chronic kidney disease. Several studies have demonstrated increased rates of early kidney disease among AI/AN, both in diabetics and non-diabetics. Among some tribes of the American Southwest, high rates of mesangiopathic glomerulonephritis have been documented. The epidemic of diabetes among AI/AN, which began in the middle of the 20th century, appears to be driving the increase in end-stage renal disease (ESRD). At the end of 1999, AI/AN had a national prevalence rate of treated ESRD that was 3.5 times greater than that of white Americans. There is significant regional variation as well as differences among the approximately 550 tribes that make up the American Indian community, with some tribes experiencing ESRD rates over twenty times the rate of whites. Although graft survival is excellent, AI/AN ESRD patients are less likely than whites to be placed on the transplant waiting list, and those listed wait longer for a transplant. Despite socioeconomic barriers and high rates of co-morbid illness, survival among AI/AN ESRD patients is better than among whites. The burden of kidney disease, particularly the multigenerational occurrence in some families, is perceived as a major threat to the well-being of native communities. There is a sense of urgency among tribal leaders to address this epidemic, and research that may decrease its burden is likely to be welcomed.

Approximately 2.5 million people identified themselves as American Indian or Alaska Native (AI/AN) in the 2000 United States census. The AI/AN population includes members of over 550 federally recognized tribes, representing diverse cultural traditions and lifestyles. Approximately 38% of AI/AN live on rural reservations, mostly in the western United States (US), and 22% live near reservations. Tribes function as sovereign nations and relate to the US federal government on a nation-to-nation basis. The Navajo Nation is the largest tribe, with 250,000 members, and a reservation in northern Arizona, western New Mexico, and southern Utah that covers more than 25,000 square miles. The American Indian population is relatively young, with a median age

of 27.8 years (vs. 35.8 years for the U.S. all races), and relatively poor with 32% living below the poverty rate (vs. 13.1% of the US population). Unemployment is twice as high as and income two thirds of that of the rest of the country; the high school dropout rate is 35% compared with 25% for the general population [1].

During the past few decades the disease burden among AI/AN has shifted from acute infectious diseases to chronic illnesses, particularly type 2 diabetes and its complications. Diabetes, virtually unknown among AI/AN people prior to World War II, is a problem of epidemic proportions among the native people of North America. Diabetes prevalence among AI/AN aged 20 to 44 years, 45 to 64 years, and over 65 years is 3.5%, 19%, and 21.5%, respectively, 2.8 times the rate of diabetes among US non-Hispanic whites [2]. Nine percent of all AI/AN aged 20 years and older are diabetic. In some tribes (for example, Pima, Zuni), 30 to 50% of the population is diabetic. Among Navajo people aged over 45 years 40% are diabetic [3]. The incidence continues to rise among all age groups, but this rise is most alarming in adolescents and young adults. From 1991 to 1997 the diabetes prevalence among AI/AN aged 15 to 19 years increased 32% [4]. Diabetes mortality among AI/AN (39.4/100,000 population) is three times higher than in the US population (13.3/100,000 population).

Most AI/AN people living on reservations and some who live in urban centers receive their health care through the Indian Health Service (IHS), an agency of the US Public Health Service. The IHS is the principal federal health care provider and health advocate for Indian people. Its goal is to raise their health status to the highest possible level. The provision of health services to members of federally recognized tribes grew out of the special government-to-government relationship between the federal government and Indian tribes. The IHS currently provides health services to approximately 1.5 million people with a budget of approximately 2.5 billion dollars. IHS services are provided directly and also through tribally contracted and operated health programs. Health services also include health care purchased from more than two thousand private providers. As of October 1998, the Federal system consisted of 37 hospitals, 59 health

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centers, 44 health stations, and four school health centers. Of 151 service units, 85 were operated by Tribes. In addition, 36 urban Indian health projects provide a variety of health and referral services. Tribal health programs also provide comprehensive preventive and curative services. As of March 1996, American Indian tribes and Alaska Native corporations administered 12 hospitals, 116 health centers, three school health centers, 56 health stations, and 167 Alaska village clinics.

BURDEN OF RENAL DISEASE

End-stage renal disease

American Indians and Alaska Natives experience high rates of end-stage renal disease (ESRD). At the end of 1999, 5361 people identified as AI/AN were being treated for ESRD, reflecting a prevalence 3.5 times greater than that of white Americans [5]. The incidence for ESRD was 2.7 times the white rate and increased at 8% per year during the period of 1992 to 1996. During the 10-year period from 1988 to 1997 the number of AI/AN with ESRD tripled. The epidemic of diabetes among AI/AN, which began in the middle of the 20th century, appears to be driving the increase in ESRD. More than two thirds (68%) of AI/AN who initiated treatment for ESRD in 1999 developed kidney failure as a result of diabetes, virtually all type 2, while only 25% of whites and 42% of blacks with ESRD were diabetic. The incidence for ESRD due to type 2 diabetes among AI/AN during 1996 to 1999 (349/million) was three times the white rate (99/million), and higher than any other disease-specific rate for any US race. The incidence was substantially higher in AI/AN women (394/million) than in men (304/million). In addition to those whose primary renal diagnosis is diabetic nephropathy, many persons with ESRD due to non-diabetic kidney disease subsequently develop diabetes. Consistent with the early onset of type 2 diabetes among native people, the mean age of onset of ESRD for AI/AN is 57 years, six years younger than for whites (63 years).

The rates cited above describe the burden of ESRD among all persons in the United States identified by their treatment facility as AI/AN. As alarming as these national rates are, they mask significant regional variation as well as differences among the approximately 550 tribes that make up the American Indian community. Analysis of 1994 data from ESRD Network #15 and the IHS shows that the burden of kidney failure is much higher among AI/AN of the Southwest, who receive their care from IHS, than it is among the US population or the national AI/AN population. ESRD Network #15, which collects data from the Southwest (Arizona, New Mexico, Colorado, Utah, Wyoming, and Nevada), includes more than 30% of the AI/AN identified in the US Renal Data System (USRDS) database and a plurality of the AI/AN

with ESRD living on reservations, primarily in Arizona and New Mexico [6]. While the overall US rate of treated ESRD was 3.2 times greater among AI/AN than among whites, in the Southwest the AI rate was 6.5 times greater. Ninety-two percent (92%) of these Southwest ESRD patients were full-blood quantum AI/AN (all four grandparents are AI/AN). Among Southwest AI, over 80% of incident ESRD is due to diabetes. At the end of the year 2000 the Navajo Nation had over 550 ESRD patients, more than any other tribe.

Some communities of the Southwest have extraordinarily high rates of kidney failure. In Zuni Pueblo, a community of 10,000 in western New Mexico, the prevalence of ESRD is 17,400 per million population [7]. This is 4.5-, 5.7-, and 21.3-fold higher than that for African Americans, American Indians, and European Americans, respectively. Approximately 2% (100 persons) of the adults aged 21 years and older in the Zuni population have treated ESRD. With rates this high, virtually every family has an affected member.

Chronic kidney disease

End-stage renal disease rates are but one reflection of the burden of kidney disease; the rate of renal disease less than end-stage is more difficult to determine. Several studies have demonstrated increased rates of early kidney disease among AI/AN, both in diabetics and non-diabetics. The Strong Heart Study, a longitudinal study to measure risk factors for cardiovascular disease among American Indians from three geographic sites (Arizona, North and South Dakota, and Oklahoma) has demonstrated high rates of abnormal albumin excretion (20.1 to 48.3%) in all tribes studied [8]. Although the prevalence of diabetes was 53% in the study population, persons without diabetes also had high rates (10 to 20%) of abnormal albuminuria. Among both diabetics and non-diabetics abnormal albumin excretion was associated with increased blood quantum (degree of Indian heritage), suggesting a genetic basis for susceptibility to renal injury. The Zuni Kidney Project, a population-based, cross-sectional survey of the Pueblo of Zuni also has demonstrated albuminuria in 20% of the population, only half of whom are diabetic [7].

Determining the burden of non-diabetic renal disease is problematic in a population where 30 to 50% of the adult population may be diabetic, because many cases of non-diabetic renal disease also may have diabetes as a co-morbid condition. In these cases nephrologic evaluation might be delayed until late in the course of the renal injury, when biopsy is no longer a consideration, and physicians may incorrectly assume that the primary cause of the renal failure is diabetes.

The prevalence and natural history of non-diabetic kidney disease among AI of the Southwest has been the subject of several published reports over the past 20 years.

Studies of Zuni Pueblo during the 1980's reported high rates of mesangiopathic glomerulonephritis (MesGN), predominantly IgA, and documented pedigrees of several families with multiple members affected in different generations [9]. A biopsy series from 44 Zuni people with non-diabetic renal disease included 34 (77%) with MesGN. Immunoglobulins and complement and well-defined electron-dense deposits were present in the mesangium in half these cases. IgM, IgA, IgG, and C3 were variably represented. A review of all AI renal biopsies processed at the University of New Mexico Health Sciences Center from 1971 to 1989 included 166 specimens; 64 of these were from Zuni. Immunoglobulin-positive MesGN, mesangial expansion and/or mesangial cell proliferation, together with mesangial immune deposits were diagnosed in 78% of the Zuni specimens. Nearly 40% showed cellular crescents [10]. The majority showed interposition of mesangial matrix material into the glomerular capillary walls, glomerulosclerosis, interstitial fibrosis, and tubular atrophy. Although these reports and anecdotal clinical reports suggest high rates of glomerulonephritis among both the Zuni and other tribes, the Zuni Kidney Project is the first population-based investigation of the burden of non-diabetic renal disease in an AI/AN community.

The burden of nephropathy among diabetics has been monitored for several years by the IHS Diabetes Program through a yearly chart audit [11], which includes measures of renal function and abnormal protein excretion. In 1999, 13,248 charts were randomly selected for audit from the 80,827 persons enrolled in the IHS Diabetes Registry. Although only 3% of these diabetics had a creatinine greater than two, nearly 50% had significant loss of renal function based on a calculated creatinine clearance: 2% with less than 20 mL/min, 19% with 20 to 59, 22% with 60 to 80, and 45% with >80 mL/min. Abnormal protein excretion was present in 33% of the patients, 10% with microalbuminuria and 23% with overt proteinuria. Hypertension was present in 77% of those with overt proteinuria and 69% of those with microalbuminuria.

TREATMENT OF ESRD

For many tribes, the epidemic burden of ESRD has become a community-wide problem, and significant efforts have gone into establishing dialysis services on reservations. The first on-reservation dialysis unit was established at Shiprock, New Mexico in 1979. At the end of 2000 there were over 30 dialysis units on or near reservations serving predominantly AI/AN patients [12]. Although reservation-based dialysis units have improved the access of patients to renal replacement therapy, enormous barriers to improving care remain. These include the rural and frequently isolated settings where travel to facilities is made difficult by distance and road condi-

tions, high rates of poverty, difficulty in recruiting and retaining staff in outlying areas, language and cultural differences, and the high numbers of patients with diabetes and extra-renal diabetic complications. A recent survey of the 524 AI/AN dialysis patients aged 20 to 60 years living in Arizona and New Mexico revealed that 80% lived on a reservation, 31% had only an elementary education, 73% did not speak English at home, and 56% traveled more than an hour each way for dialysis treatment. Common co-morbid conditions included diabetes (73%), hypertension (83%), peripheral vascular disease (44%), blindness (30%), and liver disease (10%) [13].

ACCESS TO TRANSPLANTATION

At the end of 1999, only 22% (1181) of the AI/AN ESRD population had functioning transplants, compared with 36% of white US ESRD patients. The rate of renal transplants for the treated AI/AN ESRD was 0.7 transplants/100 patient-years on dialysis, while the rate for white patients was 1.8 transplants/100 patient-years on dialysis. Transplant rates among diabetic ESRD patients are similarly disproportionate: 0.4/100 patient-years on dialysis for AI/AN and 0.9 for US whites. According to the Health Care Financing Administration AI/AN ESRD patients are less likely than whites to be placed on the transplant waiting list, and those listed wait longer for a transplant. Similar results were found in studies by ESRD Network #15 of AI/AN ESRD patients in Arizona and New Mexico, who have lower transplant rates than whites in both states, even when rates are adjusted for diagnosis and age [13]. Delays in completing transplant evaluations play a significant role in the low access to transplantation for at least some racial and economic minorities. ESRD Network #15 and the IHS examined socio-demographic factors, ESRD treatment, co-morbidities, and transplant candidacy status to determine the factors that contribute to candidacy and whether the AI/AN ESRD population experiences barriers not encountered by the white population. Using six different criteria, they showed that the rates of candidacy for AI/AN and white ESRD patients were about the same by every definition except the most stringent: awaiting transplant. Thus, AI/AN are referred for transplant at similar rates as white patients, but experience a greater delay before transplantation.

The major barriers to transplantation for AI/AN ESRD patients lie in the process of fulfilling requirements and in the availability of matching kidneys. Data obtained from the United Network for Organ Sharing (UNOS) indicate that the Kaplan-Meier median waiting time to transplant for patients from Arizona and New Mexico listed during 1997 through 1999 was 1306 days for AI/AN and 929 days for whites. After six months on the waiting list 6.2% of the AI/AN patients and 11.1% of white pa-

tients had received a transplant. Although a higher proportion of AI transplant recipients in ESRD Network #15 have a living-related donor allograft than white recipients, cadaver donation from AI/AN remains a rare event. Significant cultural barriers will have to be overcome to increase the donation rate.

Unlike African Americans, another racial minority with low transplant rates, graft survival in AI/AN compares favorably with that of whites. UNOS reports that both patient and graft survival were slightly, though not statistically, better among AI/AN than among whites in Arizona and New Mexico during 1997-1999.

SURVIVAL WITH ESRD

Despite socioeconomic barriers and high rates of comorbid illness, survival among AI/AN ESRD patients is better than among whites. The USRDS reports a mortality rate for prevalent dialysis patients in 1999 of 196.7/1000 patient-years for whites and 162.4/1000 patient-years for AI/AN. Although the mean albumin of AI/AN persons starting dialysis from 1995 to 2000 (3.0 g/dL) was lower than for whites (3.2 g/dL), body mass index, which also may predict survival, was higher (26.8 kg/m²) than for whites (25.8 kg/m²). Survival among AI dialysis patients of ESRD Network #15 appears to be better than USRDS rates. Although network-specific mortality rates have not been calculated, virtually all of the facilities serving native patients have standardized mortality ratios (SMR) of less than 1.0, several with SMRs much lower. In 2001, the SMRs of the six facilities serving the Navajo Nation range from 0.37 to 0.94. This was particularly remarkable because the mean albumin of all AI/AN dialysis patients in Network #15 was 2.81 g/dL, 10% lower than the mean of all Network #15 patients, 3.12 g/dL.

PREVENTION/EARLY INTERVENTION

Diabetes is the predominant cause of the excess burden of ESRD among AI/AN, and the IHS has committed significant resources over the past 30 years to address diabetes and its complications. Despite per capita funding of only 40% of what is provided for the US civilian population through private insurance and other programs (\$1578 vs. \$3920/year), the IHS, a public health agency providing comprehensive care to AI/AN, has been aggressive in implementing and monitoring optimal care for diabetics at risk for progressive renal disease.

A review of 13,248 charts randomly selected from the 80,827 persons enrolled in the IHS Diabetes Registry in 1999 demonstrated that IHS providers were more successful in achieving benchmarks of clinical care for diabetic nephropathy than other large providers [11]. Of the 13,248 patients reviewed, 67% were hypertensive. Of these, 67% were being treated with an ACE inhibitor;

and blood pressure was controlled in 62%: 16% achieved "Ideal BP Control" (<120/<80 mm Hg), 22% "Target" BP (120 to <130/80 to <85 mm Hg), and 24% "Adequate Control" (130/85 to <140/<90 mm Hg). Approximately 30% had "Inadequate" control (140/90 to <160/<95 mm Hg) and 8% had markedly poor control (160/95 mm Hg or higher). In aggregate, blood pressure was controlled in 62% of diabetics compared to 27% of the US hypertensive population. Of the total number of diabetic patients reviewed, over 80% had a creatinine determination and urinalysis within the past year, and over 75% had a lipid evaluation. Sixty-three percent of patients with abnormal protein excretion and 73% of persons with abnormal protein excretion and hypertension were treated with an angiotensin converting enzyme (ACE) inhibitor.

The effectiveness of the IHS in achieving this level of care suggests the potential benefit of approaching kidney disease using a public health model. Such a model includes a multi-disciplinary clinical approach integrated with community-based interventions. These interventions include preventive measures involving environmental, educational, and outreach activities, and combine with the therapeutic measures into a comprehensive health service delivery system.

FUTURE RESEARCH

Even with highly effective intervention programs, the burden of ESRD will continue to increase among AI/AN. AI/AN communities are often considered as subject populations for research because they are relatively easy to identify, have high rates of specific diseases, and are highly endogamous. The epidemic of type 2 diabetes that has affected AI/AN communities for 50 years is now being duplicated in other "emerging" groups worldwide and in the populations of highly industrialized countries, suggesting that AI/AN are not an aberrant group but merely "ahead of their time." The natural history of diabetic nephropathy has been well studied in the Pima Indians and has been utilized in understanding other populations. Native health leaders frequently express the desire that further efforts will be made to research effective preventive interventions that will have a similar wide application.

Some research questions that could be addressed in the near future include:

Is there increased susceptibility to non-DM renal injury among AI/AN?

Why is the incidence of ESRD increasing among AI women with diabetes?

Why is survival on dialysis better for AI/AN than for nonAI/AN populations despite low initial albumin?

What is the most cost effective way to deliver care to persons with CKD in high-risk populations?

Although many tribes have had negative experiences with outside researchers in the past, well-conducted research efforts that can demonstrate a potential benefit to native communities are supported by tribes. Tribally controlled institutional review boards promote such research while ensuring rigorous protection of community members who are potential research subjects. Tribes generally reserve the right to review manuscripts prior to publication to insure that their community is not identified in a way that they believe is inappropriate. Investigators who wish to pursue questions such as those listed above are most likely to be successful if they view tribal leadership and the community as partners in research, not just subjects. The burden of kidney disease, particularly the multigenerational occurrence in some families, is perceived as a major threat to the well-being of native communities. There is a sense of urgency among tribal leaders to address this epidemic, and research that may decrease its burden is likely to be welcomed.

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